

An der Chirurgischen Klinik mit Poliklinik
der Universität Erlangen-Nürnberg
Direktor: Professor Dr. G. Hegemann

STUDIEN ÜBER DEN HYPERCALCÄMISCHEN EFFEKT VON INTRAVENÖSEM SEKRETIN BEIM MENSCHEN

Inaugural - Dissertation
zur Erlangung der Doktorwürde
dem Fachbereich Medizin
der Friedrich-Alexander-Universität
Erlangen-Nürnberg

vorgelegt von
Paul-Ernst Kayser
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Studies on the Calcemic Effect of Intravenous Secretin in Humans

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The blood sugar only rose in the experiments with glucagon infusion and the serum gastrin level during gastrin application. No correlation to the occurrence of gastrointestinal symptoms was found (Fig. 1).

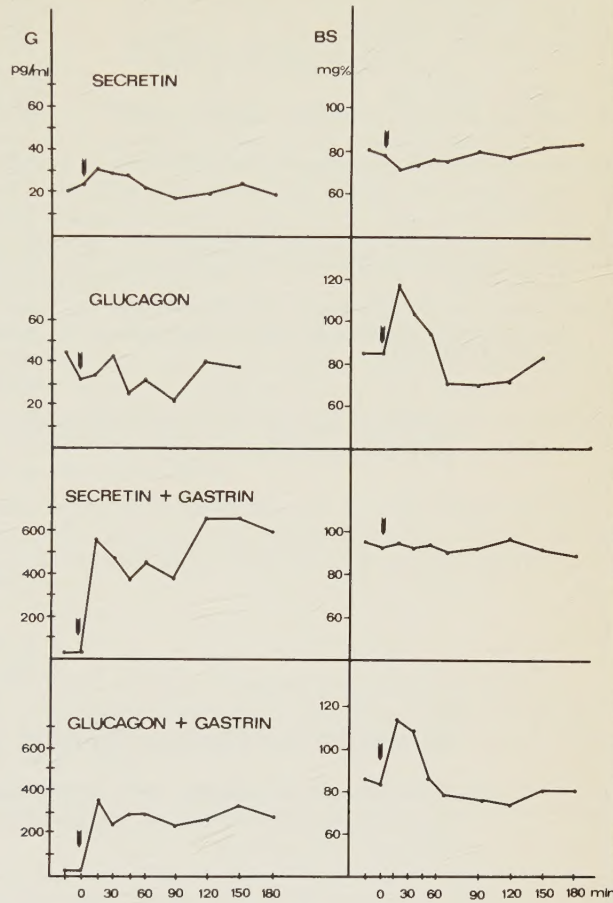


Fig. 1. Serum gastrin (G) and blood sugar (BS) levels during the infusions. $\downarrow$ = start.

Discussion

We conclude from our study that secretin alone is not the hormone responsible for the diarrhea in the Verner-Morrison syndrome, because no diarrhea occurred with infusion of this hormone. When calculating the serum secretin concentration obtained by the infused amount of secretin the value should be higher than the reported normal serum secretin level of 100 pg/ml (5). Furthermore, a combined infusion of secretin and gastrin brought on no diarrhea in the subject while diarrhea occurred with a combination of glucagon and gastrin as described by *Barbezat and Grossman* in dogs (1, 4). The action of glucagon and secretin is the same in several organs probably due to the similar chemical structure (6, 9) but in other organs the two hormones are contraacting, e.g. in pancreatic and small intestinal secretion (3, 7, 8). This different action on the small intestinal secretion could explain why the combined infusion of gastrin and glucagon induces diarrhea while that of gastrin plus secretin does not.

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Summary

In healthy controls ($n = 7$), patients with duodenal ulcer ($n = 7$), primary hyperparathyroidism ($n = 7$), and 1 case of excluded gastric antrum the effects of intravenous secretin ("Karolinska"; 3 U/kg/h for 90 min) upon serum calcium fractions, total protein, and the integrated response of gastrin and glucagon were investigated. In all groups total calcium, total protein, and protein-bound calcium fraction rose significantly but the ionized calcium fraction remained stable. Since serum concentration of gastrin and glucagon could not be altered in any of the groups a direct interference of these hormones with calcium homeostasis during secretin infusion can be ruled out. Hyperparathyroid patients had higher baseline glucagon values (209 ± 30 pg/ml) than normals (127 ± 6 pg/ml) and ulcer patients (138 ± 11 pg/ml) and maintained a higher hormone output throughout the experiment.

Zusammenfassung

Bei Gesunden ($n = 7$), Patienten mit Duodenalulcus ($n = 7$), primärem Hyperparathyreoidismus ($n = 7$) und 1 Patient mit exkludiertem Magenantrum wurden die Wirkungen von intravenösem Sekretin („Karolinska“; 3 Einheiten/kg/h während 90 Minuten) auf die Calciumfraktionen im Serum, das Gesamteiweiß und die integrierte Antwort von Gastrin und Glucagon untersucht. In allen Gruppen kommt es zu einem signifikanten Anstieg von Gesamtcalcium, Totalprotein und proteingebundenem Calcium, während der ionisierte Anteil des Serumcalciums konstant bleibt. Gastrin und Glucagon änderten sich in keiner Gruppe signifikant, womit eine Interferenz dieser Hormone mit dem unter Sekretin veränderten Calciumstoffwechsel ausscheidet. Patienten mit Hyperparathyreoidismus hatten höheres Nüchtern-glucagon (209 ± 30 pg/ml) als Gesunde (127 ± 6 pg/ml) und Ulcuspatienten (138 ± 11 pg/ml) und

Together with data on the patient with excluded antral parts it is concluded that the hypercalcemic effect of secretin is not mediated by calcium-regulating hormones but must be of an unspecific nature.

unterhielten eine höhere Hormonproduktion während des Experimentes. Zusammen mit den Daten bei exkludiertem Antrum kann festgestellt werden, daß der hypercalcämische Sekretineffekt nicht durch Calcium-regulierende Hormone vermittelt wird, sondern von unspezifischer Natur sein muß.

Key-Words: Secretin – Hypercalcemia – Gastrin – Glucagon – Calcium fractions – Excluded antrum

Very recently *Isenberg, Brickman and Moore* (12, 13) described a hitherto unknown increase of serum calcium during intravenous administration of secretin into healthy controls, hyperparathyroid (HPT), and Zollinger-Ellison (ZE) syndrome patients. Moreover, they also described a rise of ionized serum calcium that was measured by a sensitive electrode, which might indicate that secretin hypercalcemia is mediated by enhanced release of parathyroid hormone (PTH).

However, the question remained unresolved by these authors as to whether these changes in calcium concentration were brought about by concomitant secretin-mediated alterations of either circulating gastrin or glucagon or both. These peptide hormones are potent stimulatory agents for thyroïdal calcitonin (CT), at least in several animal species (5, 26), which in turn may inhibit bone resorption and lead to hypocalcemia (27). Conversely, hypercalcemia could be expected as a result of deinhibition of bone resorption in case of suppressory activity of exogenous secretin upon release of gastrin and/or glucagon.

Therefore, in order to elucidate the nature of secretin hypercalcemia in more detail, we re-evaluated its effect upon fasting serum gastrin, glucagon, and calcium fractions with special regard to ionized calcium in healthy controls, patients with duodenal ulcer disease, and those with primary hyperparathyroidism (HPT).

Patients and Methods

1. Controls: healthy volunteers; $n = 7$; 5 ♂, 2 ♀; 23 to 32 years. This group comprised members of the laboratory staff and medical students. A 12-channel multiscreening (Autoanalyzer, Technicon) yielded normal values in each. Analysis of gastric secretion: basal acid output (BAO) 2.17 ± 0.86 mval/h (mean $\pm$ SEM); pentagastrin-stimulated peak acid output (PAO) 25.7 ± 4.71 .
2. Ulcus duodeni: $n = 7$; 7 ♂; 30 to 60 years. In all cases the diagnosis was ascertained by prior endoscopy, biopsy and X-ray examinations. None of them had been surgically treated previously. BAO 6.47 ± 1.94 ; PAO 37.05 ± 2.70 .
3. Primary hyperparathyroidism (HPT): $n = 7$; 3 ♂, 4 ♀; 42 to 65 years. The leading biochemical abnormalities were hypercalcemia (total calcium in 5 cases, isolated elevation of the ionized fraction in 2 cases) and increased urinary cyclic AMP in all patients. Clinical diagnosis was confirmed in all patients: surgical removal of a single adenoma (6 cases) and chief cell hyperplasia of 3 glands (1 case). BAO 2.82 ± 0.53 ; PAO 26.6 ± 2.17 .
4. Excluded antrum (patient L., J.): during various surgical procedures a greater part of gastric antrum was left behind, which led to a rise in fasting gastrin (355 pg/ml) and persistent abdominal ulcer-like pains. BAO 2.97; PAO 6.44 mval/h. He was cured by resection of antral parts.

Following a 12-hr overnight fast all experiments were done in a supine position and urinary bladder was voided immediately prior to the test. Pure natural secretin (Karolinska, Stockholm) was i.v. infused (3 U/kg for 90 min (12) in 300 ml of 0.15 M saline. Venous blood was drawn on the contralateral side as following -20, -10, 0, 7.5, 15, 20, 45, 60, 75, 90, 120 min. Calcium, inorganic phosphate and sodium excreted during the experiment were determined from aliquots of the urine voided after 150 min.

Analyses: total (Ca_T) and ultrafiltrable (Ca_D) calcium by complexometric titration ("Marius" titrator; Kipp GmbH, Schönberg). Ionized fraction (Ca^{++}) according to the modification by Wills (30) of the double wave length method (17) using ultrafiltrate (37°C) and tetramethylmurexide as pH-independent indicator. All specimens were analyzed the same day (Zeiss PMQ II, microcuvette, 480 and 540 nm). Precision criteria: intrassay coefficient of variation (c.v.) 2.26; recovery (accuracy) 95.5 to 112% within a range of 4 to 10 mg/100 ml (c.v. 1.02-3.75). Protein-bound calcium (Ca_{prot}) was calculated by difference ($\text{Ca}_T - \text{Ca}_D$), ultrafiltrates were produced in a system of closed chambers (Millipore GmbH, Neu-Isenburg) as earlier described (22), total serum protein, urinary phosphate, sodium, and creatinine by conventional methods.

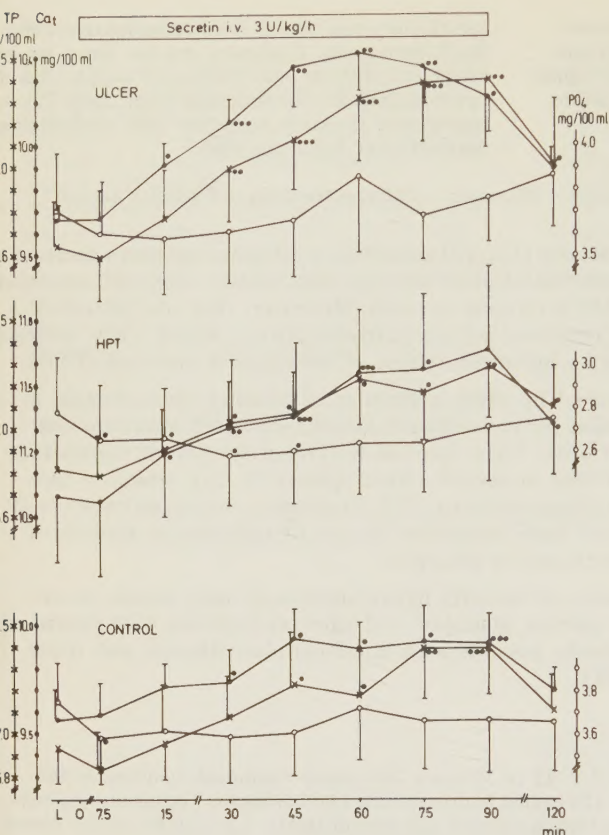


Fig. 1. Changes of total calcium (Ca_t), total protein (TP) and inorganic phosphate (PO_4) in plasma of healthy volunteers (controls), hyperparathyroid (HPT) and duodenal ulcer (ulcer) patients during i.v. secretin. Mean $\pm$ SEM. L = baseline (mean of 3 preexperimental values).

$\cdot$: $p < 0.05$; $\cdot\cdot$: < 0.01 ; $\cdot\cdot\cdot$: < 0.005

Radioimmunoassay for gastrin and glucagon was set up using synthetic Human Gastrin I (Imperial Chemical Industries Ltd., Heidelberg) and recrystallized porcine glucagon (Lilly Corp., Indianapolis, Ind.) as standard substances. Antibody 30 K (supplied by Dr. R.H. Unger, Dallas, Tex.) was used for measurement of pancreatic glucagon (1); gastrin antibody was raised in rabbits against human 2-17 heptadecapeptide. Both antibodies failed to crossreact with other gastrointestinal hormones. Intraassay and interassay c.v. in the same sample were 6.0 and 7.5 (gastrin), 10.0 and 12.6 (glucagon). The integrated response of each hormone was calculated according to *Stadil and Rehfeld* (25) and the differences between groups were statistically evaluated (Student's test for unpaired data). Differences between baseline and experimental values of other plasma parameters were examined using the test for paired data.

Results

Calcium: in all groups secretin effects a remarkable rise of Ca_t (Fig. 1), but also a comparable one of plasma total proteins. Quantitatively the former is less pronounced in the control group (approximately 0.45 mg/100 ml; 45 min) than in HPT (90 min) and u.d. (90 min), each showing a mean increment of 0.75 mg/100 ml. Regression analysis yielded a highly significant ($p < 0.001$) correlation between the variables Ca_t (dependent) and total protein (independent): controls $r = 0.90$; u.d. $r = 0.91$; HPT $r = 0.98$. But yet a higher correlation is obtained between protein-bound calcium and total protein in the u.d. group only (Fig. 2). Inorganic plasma phosphate dropped slightly in HPT patients (45 min) and controls (75 min), and remained stable in the u.d. group. This result suggests that the steady rise of Ca_{prot} could account for the major part, if not all, of the increment in Ca_t , whereas the uncharacteristic pattern of Ca_D can in no way reflect it (Table 1). Baseline Ca^{++} values agree well with our results measured with a sensitive electrode (22, 23) (Table 1), but following secretin this decisive fraction also remained stable in each group, thus precluding an exaggerated release of PTH.



Fig. 2. Relationship between plasma total protein and protein bound calcium in healthy controls (●), ulcer (▲) and hyperparathyroid (○) patients.

Controls: $Y = 0.29 X + 1.5$; $r = 0.35$; n.s.

HPT: $Y = 1.99 X - 9.6$; $r = 0.90$; $p < 0.00$

ulcers: $Y = 0.61 X - 0.51$; $r = 0.96$; $p < 0.00$

2. Gastrin: fasting values were 88 ± 7 pg/ml (controls), 98 ± 7 pg/ml (HPT), and 106 ± 7 pg/ml (ulcer). During secretin there was a slight but insignificant mean fall of gastrin in controls (60 min, 5 pg/ml) and the u.d. group (4 pg/ml), confirming earlier results of *Schrumpf and Myren* (20) in patients with gastric carcinoma. Although gastrin in HPT rose slightly (30 min, 16 pg/ml) these differences in our assay system do not allow statistical evaluation of the influence of exogenous secretin upon endogenous gastrin. Most of the differences can be fully explained by the variance of repeated assay procedures. In addition, integrated gastrin response revealed no differences between groups at any time of the experiment (Fig. 3).

3. Glucagon: fasting values were 127 ± 6 pg/ml (controls), 138 ± 11 (u.d.), and 209 ± 30 (HPT). The HPT values are significantly higher than those in controls and confirm our earlier findings that HPT must in some way be related to the functional activity of pancreatic islets (23). In all groups secretin induces a small but insignificant rise in glucagon. Conversely, glucagon integrated for 90 min (Fig. 3) shows that the alpha cells in HPT maintain a relatively high hormone output throughout the whole experiment.

4. Excluded gastric antrum, resulting in high baseline gastrin because of the lack of G-cell inhibition by acid secretion from the stomach (15), seemed to be a suitable model for studying whether or not secretin action upon calcium was mediated by simultaneous suppression of serum gastrin. Fig. 4 outlines all relevant data of this patient: also a sharp fall in gastrin cannot

Table 1. Ionized (Ca⁺⁺), ultrafiltrable (Ca_D) and protein bound (Ca_{prot}) calcium during secretin infusion. Mean ± SEM; L: mean of 3 control values; *: time (min) following start of infusion; (): number of patients

	L	7.5'	15'	30'	45'	60'	75'	90'	120'
secretin i.v. 3 U/kg/h									
Controls (7)									
Ca ⁺⁺	4.52 0.06	4.80 0.28	4.47 0.12	4.64 0.23	4.64 0.19	4.81 0.22	4.58 0.22	4.86 0.26	4.58 0.18
Ca _D	6.04 0.12	6.04 0.05	6.49 ^o 0.22	6.21 0.27	6.18 0.27	6.47 ^o 0.24	6.36 0.25	6.23 0.19	5.91 0.21
Ca _{prot}	3.54 0.19	3.56 0.14	3.23 0.17	3.54 0.24	3.75 0.28	3.43 0.26	3.50 0.22	3.69 0.14	3.75 0.24
HPT (7)									
Ca ⁺⁺	5.37 0.29	5.65 0.41	5.20 0.21	5.26 0.30	5.30 0.24	5.44 0.42	5.09 0.20	5.29 0.27	5.43 0.38
Ca _D	7.03 0.31	7.11 0.27	6.84 0.24	7.02 0.31	7.11 0.24	6.90 0.25	6.59 ^o 0.18	6.71 0.27	6.93 0.36
Ca _{prot}	3.97 0.26	3.87 0.17	4.35 0.15	4.28 ^o 0.28	4.25 0.19	4.65*** 0.24	4.99*** 0.37	4.96*** 0.40	4.40* 0.32
Ulcer duodeni (7)									
Ca ⁺⁺	4.45 0.15	4.52 0.16	4.46 0.15	4.49 0.14	4.64 0.15	4.77 0.20	4.53 0.14	4.61 0.13	4.49 0.12
Ca _D	6.14 0.07	6.27 0.14	6.19 0.22	6.33* 0.06	6.40 0.11	6.51* 0.12	6.35 0.11	6.22 0.10	6.12 0.09
Ca _{prot}	3.52 0.13	3.49 0.21	3.72 0.18	3.77* 0.12	3.97* 0.13	3.92 0.21	4.01 ^o 0.21	4.01 ^o 0.17	3.77 0.14

^o: p = 0.05; *: < 0.05; ***: < 0.005

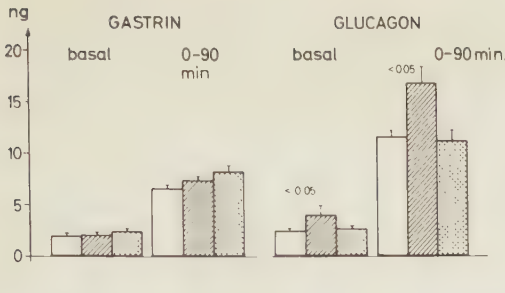


Fig. 3. Integrated output (ng) of plasma gastrin and glucagon before (basal) and during (0-90 min) intravenous secretin administration. Mean $\pm$ SEM.
 □ controls; ▨ HPT; ▤ ulcer disease

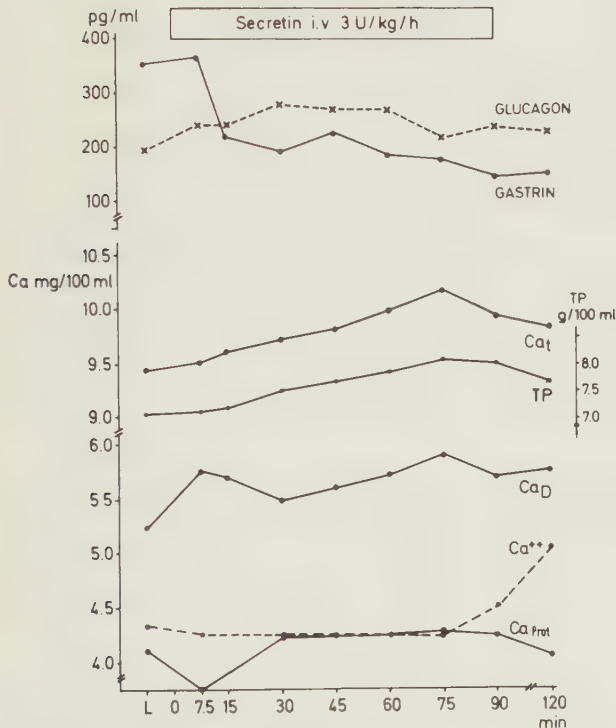


Fig. 4. Effects of i.v. secretin upon plasma concentration of glucagon, gastrin, total protein and total, ultrafiltrable, ionized and protein bound calcium in patient L.J. with excluded gastric antrum. Symbols s. Fig. 1 and Table 1.

add further to the increase in Ca_t (0.6 mg/100 ml) as compared with the one observed in u.d. patients (see Fig. 1). Again there is a close correlation between total protein and Ca_t ($r = 0.97$, $p < 0.001$).

Discussion

In humans knowledge is still scarce on interrelations of gastrointestinal hormones, CT, and PTH. Exogenous secretin inhibits gastric acid secretion in dogs (21) and may suppress fasting and postprandial gastrin in u.d. and ZE patients (28), normals (16), those with gastric carcinoma (20) and in situations with excluded antrum (15). If CT liberation in humans was, as it is in animals, related to natural stimuli such as gastrin or glucagon (26), a progradient disappearance from the circulation of one or both hormones could be considered responsible for the rise in serum calcium as a result of deinhibition of bone resorption owing to a lack in CT release from the thyroid. In vivo studies in humans led to discussion of a direct action of CT upon parathyroid tissue (6), i.e. enhanced liberation of PTH. But hypercalcemia by means of excess

Table 2. Urinary calcium, phosphate and sodium per 150 min/0.1 g creatinine during secretin infusion; mean $\pm$ SEM. (): number of patients

	Calcium mg	Phosphate mg	Sodium mval
Controls (7)	13.9 2.2	25.2 4.9	13.8 2.0
HPT (7)	39.2 10.9	44.2 4.8	26.0 5.9
Ulcus duodeni (7)	14.3 4.8	29.7 8.5	11.8 1.6

CT, conversely, would require prior secretin-induced elevation of gastrin and glucagon levels. The original authors (12, 13) assumed hormonal events like these to be operative, but there are several arguments against a direct interference of exogenous secretin with hormones normally regulating calcium homeostasis. First, there is no definite decrease in fasting gastrin in all three groups (Fig. 3), despite the presence of significantly elevated calcium levels in each, and only a slight glucagon rise in controls and in the case of excluded antral parts (Fig. 4). Thus CT neither on a higher nor lower level than during baseline may be involved in achieving hypercalcemia during secretin infusion. Second, ionized calcium remains stable throughout the experiment in all individuals, which disproves that PTH release has occurred. Third, urinary excretion of phosphate, calcium and sodium by extrapolation would yield normal daily excretion rates in controls and u.d. patients. HPT patients show higher rates for all three substances (Table 2), but these findings are not surprising in the face of proven natriuretic activity of PTH (9). Finally, there are earlier observations whereafter total serum proteins would be decreased in HPT (8), but during this study a uniform increase can be documented.

In support of this interpretation are the data collected from the patient with high baseline gastrin caused by excluded antral parts. Obviously the degree of gastrin suppressibility by secretin is limited by the gastrin concentration existing preexperimentally. This assumption could be confirmed by a recent experiment in dogs (10). Moreover, *Isenberg et al.* (12) and *Bradley et al.* (4) reported secretin elevated calcium even in ZE patients, a disorder in which gastrin rises remarkably in response to secretin, thus allowing a differential diagnosis to excluded gastric antrum (15).

No conclusive study is available on the interactions of gastrin with glucagon. According to several authors (14, 23) gastrin must be considered as a stimulus for glucagon, but at least exogenous glucagon proved to be a potent suppressor of endogenous gastrin (11). Our data documenting a secretin-induced fall of gastrin and a simultaneous rise in glucagon when antral parts are excluded (Fig. 3) would favor the existence of a negative feedback mechanism linking both hormones. Thus far they agree with results of *Dudl et al.* (7) but are at variance with those of *Santeusano et al.* (18, 19) who found a marked glucagon fall in dogs.

For further work it might be of interest whether similar results can be obtained by infusing, instead of pure natural secretin, the synthetic material which is said to markedly suppress fasting gastrin in dogs (28). But as far as the properties of recently discovered polypeptide contaminations in extracts from the upper intestinal wall are concerned, a calcemic activity in humans could not as yet be demonstrated (32, 18, 19). Earlier work revealed that as the dose of secretin was increased, considerable amounts of electrolytes and fluids were secreted from the pancreas and bile ducts into the intestinal lumen (31), indicating that some degree of contraction of extracellular volume must have occurred. Unfortunately, in this study the rates of pancreatic and intestinal secretion and reabsorption or extracellular space itself could not be measured. Nevertheless regression analyses of Fig. 2 support the view of others (29, 2) that with the same dose there might be a difference in response between healthy normals, patients with hyperparathyroidism, and those with ulcer disease. Summarizing our findings, this interpreta-

tion seems to be the most attractive in explaining the relatively higher surplus of total calcium and protein in the latter two groups. Therefore, in the face of endogenous secretin concentration, now established to range between 10 and 25 pg/ml in normals and duodenal ulcer disease patients (3), a biological role for secretin in calcium homeostasis of humans cannot be considered.

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REVIEW

Electro-Potential Differences in the Gastrointestinal Tract

Present Status*

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1. Introduction

Our limited comprehension of the continuum of physical change in the functioning digestive tract reflects the problem of observing and recording physiological events without disturbing them. Neither physical or chemical monitoring, nor radiology have provided a comprehensive view of normal function. This may explain a recent upsurge of interest (3) in the measurement of the transmural electro-potential difference (p.d.) in the gastrointestinal tract, even though the electromotive forces may remain obscure. Gastroenterologists who are unfamiliar with the technique may well wonder whether p.d. measurement is mere physiological exuberance, or whether it has an evolving clinical role. At this point in time, an appraisal of the present status of p.d. measurement is appropriate but difficult; the critic reviews the past in the knowledge that he may be confounded by the future.

Epithelial tissues are the interface between the 'milieu interieur' and the external world; a general property of epithelial layers is electrical polarisation across the layer. The orientation and magnitude of this polarisation varies with the site and function of the epithelium. Physiologists are interested in electrical changes in relation to solute and solvent transfer across epithelial layers. Clinicians see the possibility that changes in electrical polarisation may signal normal and abnormal events at the site of measurement, or elsewhere in the body, even though the underlying electrical processes may be ill-understood. In considering recent progress in this field, a minimum understanding of the theory and measurement of p.d. is useful.

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Lebenslauf

Am 30. August 1947 wurde ich als Sohn der Eheleute Rolf Kayser, Architekt, und Helga geb. Langenbach, Landgerichtsrätin, in Herborn/Dill geboren.

Ostern 1954 wurde ich in die Volksschule Herborn/Dill eingeschult, und Ostern 1958 erfolgte der Eintritt in das Gutenberggymnasium in Wiesbaden. Am 19. Juni 1967 legte ich die Reifeprüfung an dem Christian-Wirth-Gymnasium in Usingen/Ts. ab. Zum Sommersemester 1968 nahm ich das Studium der Zahnmedizin an der Universität Erlangen - Nürnberg auf, das ich am 26. Juni 1973 dort mit dem Staatsexamen abschloß.

Zur Zeit bin ich Student der Humanmedizin im 4. klinischen Semester an der Johannes-Gutenberg-Universität in Mainz.

